Paper No. 22

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte BRUCE RONSEN AND RAGAB EL-RASHIDY

Appeal No. 2001-1933
Application No. 08/940,058

HEARD: January 24, 2002

Before WINTERS, WILLIAM F. SMITH[1] and MILLS, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-37, which are the claims on appeal in the application.

We reverse.

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[1] Judge Smith has been substituted for Judge Scheiner, who was present at the oral hearing but who is unavailable at the time of this decision. Compare, In re Bose Corp., 772 F.2d 866, 868, 227 USPQ 1, 3-4 (Fed. Cir. 1985)

Claim 1 is illustrative of the claims on appeal and reads as follows:

1. A solid, stabilized amorphous paroxetine composition which comprises amorphous paroxetine hydrochloride and at least one hydroxyl-bearing compound.

The prior art references relied upon by the examiner are:

Tovey	4,493,822	Jan. 15,1985
Barnes et al. (Barnes)	4,721,723	Jan. 26,1988
Ares	5,399,584	Mar. 21, 1995
Leonard	5,811,436	Sep. 22, 1998
Francese et al. (Francese)	WO 95/15155	Jun. 08, 1995
Pathak et al. (Pathak)	WO 95/16448	Jun. 22, 1995
European Patent Application		
Damani et al. (Damani)	0 212 641	Aug. 22, 1986
United Kingdom Patent Application		
Jacewicz et al. (Jacewicz)	2 297 550	Aug. 07, 1996

Borodkin et al. (Borodkin), "Interaction of Amine Drugs with a Polycarboxylic acid Ion-Exchange Resin," Journal of Pharmaceutical Sciences, Vol. 59, No. 4, pp. 481-486 (1970)

Lieberman et al. (Lieberman), Pharmaceutical Dosage Forms – Tablets, In Three Volumes, 2nd Ed., Revised and Expanded, Vol. 2, Marcel Dekkar, Inc., publisher. pp. 462-463 (1989)

Lin et al. (Lin), "Solid particulates of drug-β-cyclodextrin inclusion complexes directly prepared by a spray-drying technique," International Journal of Pharmaceutics, Vol. 56, pp. 249-259 (1989)

Kai et al. (Kai), "Oral Absorption Improvement of Poorly Soluble Drug Using Solid Dispersion Technique," Chem. Pharm. Bull., Vol. 44, No. 3, pp. 568-571 (1996)

Uekama et al. (Uekama), "Inhibitory Effect of 2-Hydroxypropyl-β-cyclodextrin on Crystal-growth of Nifedipine During Storage: Superior Dissolution and Oral Bioavailability Compared with Polyvinylpyrrolidone K-30," J. Pharm. Pharmacol., Vol. 44, pp. 73-78 (1991)

Traue, “Spray Embedding of Low-solubility Drugs Part 3: Release of Active Ingredient From Nitrazepam-Polyvinylpyrrolidone Solids Dispersions,” Acta Pharm. Technol., Vol. 35, No. 3, pp. 155-159 (1989)

Byron et al. (Byron) "Drug Carrier Selection - Important Physicochemical Characteristics,” Respiratory Drug Delivery V, Program Proc, [Int. Symp.], pp. 103-113 (1996)

Matsuda et al. (Matsuda), "Amorphism and Physicochemical Stability of Spray-Dried Frusemide,” J. Pharm. Pharmacology, Vol, 44, pp. 627-633 (1992)

Grounds of Rejection

I. Claims 1-3, 15-17 and 25-27 stand rejected under 35 U.S.C. § 103(a) as obvious over Leonard in view of Borodkin, Lieberman, Kai or Matsuda.

II. Claims 1, 15, 16 and 32 stand rejected under 35 U.S.C. § 103(a) as obvious over Jacewicz in view of Lieberman, Kai or Matsuda.

III. Claims 1 - 37 stand rejected under 35 U.S.C. § 103(a) as obvious over Leonard, Jacewicz, Barnes, Pathak in view of Lieberman, Kai or Matsuda in further view of Lin, Traue, Uekama, Byron, Ares, Francese, Damani, or Tovey.

DISCUSSION

In reaching our decision in this appeal, we have given consideration to the appellants’ specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the noted rejection, we make reference to the examiner's

Answer for the examiner's reasoning in support of the rejection, and to the appellants' Brief and Reply Brief, for arguments thereagainst. As a consequence of our review, we make the determinations which follow.

Prior to discussion of the rejections in the application, we note that the examiner has made review of the record difficult for the following reasons. First, the examiner has referenced multiple prior papers (Paper Nos. 8 and 10) in setting forth the statement of rejection. Answer, page 4. Manifestly, this is improper. In relevant part, the Manual of Patent Examining Procedure (MPEP) § 1208 (6th ed., July 1996), states "[a]n examiner's answer should not refer, either directly or indirectly, to more than one prior Office action."

Secondly, the examiner has not relied or obtained a full text copy of the cited reference articles abstracted. Obviousness determinations are fact-intensive. It stands to reason that full text documents, whether they be English language translations of foreign language documents or full text documents will provide more facts. It is not apparent why the examiner and appellants have satisfied themselves with determining patentability under 35 U.S.C. § 103 on less than a complete factual record. We have obtained the full copies of the abstracted articles relied on by the examiner and render this decision based on the full text articles. Finally, the examiner has failed to provide an indication as to why individual claims appropriately argued by appellants are unpatentable, and has failed to respond to appellants argument as to why the claims of the application stand or fall separately. Although any one of the above difficulties would

suffice as appropriate grounds to remand the application to the examiner for further consideration, we conclude that the rejections before us are without merit rather than remand the application for further consideration by the examiner.

I. 35 U.S.C. § 103(a)

Claims 1-3, 15-17 and 25-27 stand rejected under 35 U.S.C. § 103(a) as obvious over Leonard in view of Borodkin, Lieberman, Kai or Matsuda.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). A prima facie case of obviousness is established when the teachings from the prior art itself would appear to have suggested the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993). An obviousness analysis requires that the prior art both suggest the claimed subject matter and reveal a reasonable expectation of success to one reasonably skilled in the art. In re Vaeck, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The examiner relies on Leonard for the disclosure of a "paroxetine hydrochloride salt and carboxylic composition (see Borodkin Amberlite IRP-88 being poly-carboxylic acid). Answer, page 4. According to the examiner, the "difference between the claims and Leonard et al. '436 is that Leonard et al. '436 used paroxetine hydrochloride in its hemihydrate crystal while the instant claims employed an amorphous form." Id.

However, as pointed out by appellants, another important difference between the composition of the Leonard and the claimed composition, is that the composition of Leonard is a liquid. Reply Brief, page 9.

The examiner further argues that, "It is known in the art that amorphous solids will in general be better absorbed than will crystalline ones (see Lieberman et al. P. 463), and the solid dispersion process i.e. spray-drying, will alter a crystalline form of a compound to an amorphous state (see Kai abst, Matsuda p. 627)." Answer, page 4.

The examiner concludes (Id.):

> Therefore, one having ordinary skill in the pharmaceutical formulation art would be motivated to employ a spray-drying process of paroxetine hydrochloride crystals of the prior art in solid formulation since it is conventionally taught that spray-drying is expect[ed] to give a better absorbed amorphous state of the drug.

To establish a prima facie case of obviousness, the examiner must show "some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). There is no suggestion to combine, however, if a reference teaches away from its combination with another source. See, id. at 1075, 5 USPQ2d at 1599. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant . . . [or] if it suggests that the line of development flowing from the reference's disclosure is

unlikely to be productive of the result sought by the applicant." In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). If when combined, the references "would produce a seemingly inoperative device," then they teach away from their combination. In re Sponnoble, 405 F.2d 578, 587, 160 USPQ 237, 244 (CCPA 1969); see also, In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984) (finding no suggestion to modify a prior art device where the modification would render the device inoperable for its intended purpose).

In response to the rejection of the examiner, appellants argue that "Leonard et al. incorporates the teaching of Barnes et al. U.S. Patent No. 4,721,723 ('436 patent, Col. 2, lines 22-24.), and thereby teaches away from using amorphous paroxetine hydrochloride. Barnes et al. expressly teaches away from the claimed invention, asserting the amorphous form of paroxetine hydrochloride as unsuitable for making stable solid pharmaceutical formulations, and thus discourages any modification by one of ordinary skill in the art. (Barnes et al., U.S. Patent 4,721,723, Col. 1, lines 46-61)." Brief, page 8.

Appellants argue that because Leonard (through Barnes) teaches away from preparing an amorphous paroxetine compound, there is no motivation for combination with secondary references teaching that amorphous drugs are better absorbed. Thus, Appellants argue that no prima facie case of obviousness is established because the combination of references is without basis and motivation. We agree.

As stated in Pro-Mold & Tool Co. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629, (Fed. Cir. 1996) (citation omitted):

> It is well-established that before a conclusion of obviousness may be made based on a combination of references, there must have been a reason, suggestion, or motivation to lead an inventor to combine those references.

In the present case, we find the examiner has failed to provide sufficient evidence of motivation for combination of the cited references in view of the teaching in the art away from amorphous forms of paroxetine compounds due to their hydroscopicity and instability. This rejection is reversed.

II. and III. 35 U.S.C. § 103(a)

Claims 1, 15, 16 and 32 stand rejected under 35 U.S.C. § 103(a) as obvious over Jacewicz in view of Lieberman, Kai or Matsuda.

Claims 1 - 37 stand rejected under 35 U.S.C. § 103(a) as obvious over Leonard, Jacewicz, Barnes, Pathak in view of Lieberman, Kai or Matsuda in further view of Lin, Traue, Uekama, Byron, Ares, Francese, Damani, or Tovey.

According to the examiner, Jacewicz describes a crystalline form of paroxetine hydrochloride. The examiner argues that it is known in the art that a solid dispersion process, spray drying will alter a crystalline form of a compound to an amorphous state, citing Kai and Matsuda. The examiner concludes that "one of ordinary skill in the pharmaceutical formulation art would be motivated to employ a spray drying process of

paroxetine crystals of the prior art in solid formulation since it is conventionally taught that spray drying is expected to give a better absorbed amorphous state of the drug." Answer, page 5.

Similar to the argument set forth herein in response to the rejection (I.), appellants argue that the art (Leonard and Barnes) provides a teaching away from the use of amorphous paroxetine in pharmaceutical compositions due to its hydroscopicity, by those of ordinary skill in the art at the time the invention was made. Appellants also argue that Byron, of record, does not evidence that "any and all formulations are suitable for spray drying" to prepare amorphous compounds Brief, pages 45-46. Byron appears to suggest that "The amorphous form collected following spray drying of lactose, trehalose and sucrose was unstable in the solid state at 25°C, reverting to the crystalline form at relative humidities $\geq$ 52%." Byron, page 109. "Exposure of spray dried mannitol to high humidity in a microcalorimeter (9) also failed to induce any observable recrystallization event leading to a deduction of 100% crystallinity." Id. Thus, it would reasonably appear that those of ordinary skill in the art would not have expected that spray drying would necessarily produce stable, amorphous compounds.

Again, we agree with appellants that the examiner has failed to provide sufficient motivation for combination of the cited references in view of the teaching away in the art, discussed herein. Nor has the examiner provided sufficient evidence of a reasonable expectation of success of obtaining stable, amorphous compounds in view of the teachings of Byron.

In addition to the relevant argument above, with respect to rejection III., appellants argue that the examiner has failed to comply with the guidelines of section 707.07(d), Manual of Patent Examining Procedure (MPEP) inasmuch as the grounds for rejection of each claim have not been delineated with the requisite reasonable degree of specificity, nor has any such rejection been properly explained. Reply Brief, page 18. The appellants fairly point out that the examiner's answer, while addressing the dependent claims generally at pages 5 and 6, does not specifically indicate the grounds for rejection of each claim with a requisite reasonable degree of specificity. We remind the examiner, in the interest of due process to appellants, that the grounds for rejection of each claim should be delineated with a requisite and reasonable degree of specificity.

We find the examiner has not established on the record before us a prima facie case of obviousness. The rejections of the claims for obviousness of the claimed invention is reversed.

Other Issue

The examiner relies on Jacewicz for the disclosure of a crystalline paroxetine hydrochloride. However, Examples 2 and 3 of Jacewicz also describe a paroxetine hydrocloride containing about 2%-5.7% of propanol by weight. See also Jacewicz, page 1, lines 15-21. Upon return of the application to the examiner, the examiner should fully consider the disclosure of Jacewicz, and the applicability of Jacewicz as a

reference applied under the principles of In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) [Under appropriate circumstances the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product.]

CONCLUSION

The rejection of claims 1-3, 15-17 and 25-27 under 35 U.S.C. § 103(a) as obvious over Leonard in view of Borodkin, Lieberman, Kai or Matsuda is reversed.

The rejection of claims 1, 15, 16 and 32 under 35 U.S.C. § 103(a) as obvious over Jacewicz in view of Lieberman, Kai or Matsuda is reversed.

The rejection of claims 1 - 37 under 35 U.S.C. § 103(a) as obvious over Leonard, Jacewicz, Barnes, Pathak in view of Lieberman, Kai or Matsuda in further view of Lin, Traue, Uekama, Byron, Ares, Francese, Damani, or Tovey is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

REVERSED

SHERMAN D. WINTERS Administrative Patent Judge	)
WILLIAM F. SMITH Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
DEMETRA J. MILLS Administrative Patent Judge	)

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